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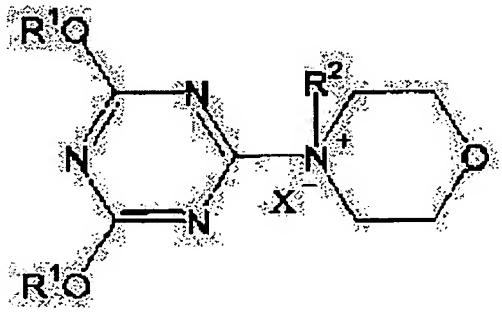
(54) WATER-CONTAINING QUATERNARY AMMONIUM SALT

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a water-containing quaternary ammonium salt capable of providing an objective substance under a mild reaction condition in a short time in a high yield, having excellent stability and to provide a method of efficiently producing the water-containing quaternary ammonium salt.

SOLUTION: A triazine compound such as 2-chloro-4,6-dimethoxy-1,3,5-triazine is reacted with a morpholine compound such as 4-methylmorpholine to give a water-containing quaternary ammonium salt comprising a quaternary ammonium salt of formula (1) (R1 is a 1-4C alkyl group or a 6-8C aryl group: R2 is a 1-4C alkyl group; X is a halogen atom) such as 4-(4,6-dimethoxy-



1,3,5- triazin-2-yl)-4-methylmorpholinium chloride, etc., and water. The water-containing quaternary ammonium salt is used as a condensation agent.

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* NOTICES *

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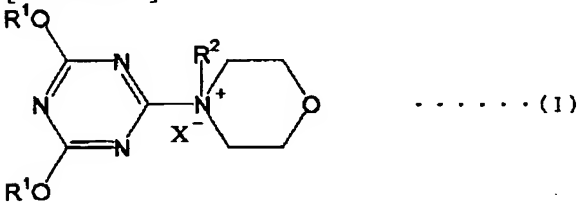
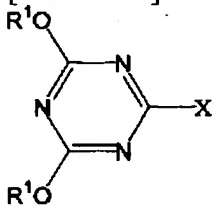
CLAIMS

[Claim(s)]
[Claim 1] The following general formula (I)
[Formula 1]



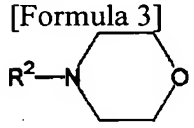
. . . . . (I)

(R1 is the alkyl group of carbon numbers 1-4, or the aryl group of carbon numbers 6-8 among a formula, R2 is the alkyl group of carbon numbers 1-4, and X is a halogen atom.) Water content quarternary ammonium salt characterized by consisting of 60 to quarternary-ammonium-salt 99 mass % shown, and 40 to water 1 mass %.
[Claim 2] The following general formula (II)
[Formula 2]



. . . . . (II)

(-- R1 is the alkyl group of carbon numbers 1-4, or the aryl group of carbon numbers 6-8 among a formula, and X is a halogen atom.) -- the triazine compound shown and the following general formula (III)
[Formula 3]



. . . . . (III)

(-- R2 is the alkyl group of carbon numbers 1-4 among a formula.) -- the manufacture approach of the water content quarternary ammonium salt according to claim 1 characterized by making the morpholine compound shown react under 0.1-10-mol existence of water and in an organic solvent to one mol of said triazine compounds.
[Claim 3] The condensing agent which consists of water content quarternary ammonium salt according to claim 1.
[Claim 4] The manufacture approach of the amide compound characterized by using water content quarternary ammonium salt according to claim 1 as a condensing agent in the approach of making a

carboxylic-acid compound and an amine compound reacting using a condensing agent, and manufacturing an amide compound.
[Claim 5] The manufacture approach of the ester compound characterized by using water content quarternary ammonium salt according to claim 1 as a condensing agent in the approach of making a carboxylic-acid compound and an alcoholic compound reacting using a condensing agent, and manufacturing an ester compound.

[Translation done.]

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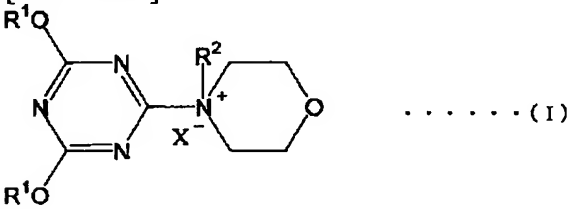
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] In case this invention manufactures an amide compound and an ester compound, it relates to the water content quarternary ammonium salt which can be suitably used as a condensing agent.
[0002]
[Description of the Prior Art] An amide compound and an ester compound are very important compounds which form the basic frame of various organic compounds, such as physic, agricultural chemicals, a color, and a high molecular compound. For this reason, the manufacture approach of an amide compound and an ester compound is considered for many years. For example, the manufacture approach of the amide compound according to the exchange reaction of an ester compound and an amine compound as the manufacture approach of an amide compound, The method of manufacturing a direct amide compound from a carboxylic-acid compound and an amine compound etc. is the especially general manufacture approach. Or as the manufacture approach of an ester compound How to manufacture a direct ester compound from a carboxylic acid and an alcoholic compound under existence of an acid, Or after making a carboxylic-acid compound and acid halogenating agents, such as a thionyl chloride, react and making carboxylic-acid chloride generate, the method of manufacturing an ester compound is the especially general manufacture approach by making it act with alcohol.
[0003] However, since the manufacture approach of an amide compound was performed to the bottom of heating, it was impossible to have applied to the compound which has an amino group and an alkoxy carbonyl group in an unstable compound or the same unstable intramolecular thermally. Moreover, since the manufacture approach of an ester compound was performed to the bottom of an acid condition, it was inapplicable to the unstable compound to the acid.
[0004] In order to manufacture an amide compound under mild conditions for the purpose of solving such a technical problem, various approaches which used condensing agents, such as a carbodiimide system, are advocated. Were especially advocated by Kaminsky and others (Z. J.Kaminski) as a condensing agent for amide compound composition. 4-(4, 6-dimethoxy-1,3,5-triazine-2-IRU)-4 - Methoxy mol HORINIUMU chloride {journal OBU organic chemistry, 63 volumes, 4248-4255 pages, and 1998(J. Org.Chem., 63, 4248-4255 (1998))} Since there is such no problem in the handling to requiring cautions that a carbodiimide system condensing agent tends to cause a rash to the skin, attention is attracted.
[0005] Moreover, about manufacture of an ester compound, the approach using the condensing agent which consists of a pyridinium oxide compound {bulletin OBU chemical SOSAIA tea OBU Japan, 50 volumes, 1863 - 1866 pages, 1977 (Bull.Chem.Soc.Jpn.), 50 volumes, and 1863 - 1866 pages (1977)} advocated by Mukoyama and others is learned as an approach of manufacturing an ester compound under mild conditions.
[0006] However, since this reactant derivative and the amine compound were made to react and the amide compound had been obtained after carrying out the equivalent reaction of a carboxylic-acid

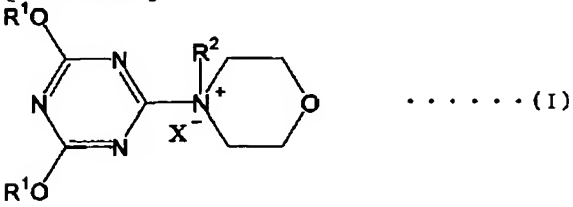
compound and this condensing agent, respectively and making the reactant derivative as intermediate field once generate by the approach advocated by Kaminsky indicated by said reference, the yield had 17 - 73%, and large dispersion, and it was not that with which satisfaction goes.
[0007] Moreover, in case this pyridinium oxide compound is manufactured to the above-mentioned pyridinium oxide compound used for manufacture of an ester compound, in order to have to use for it the methyl iodide carcinogenic is indicated to be, the problem that careful attention had to be paid was in work environment.
[0008] Then, this invention persons are the following general formulas (I), as a result of inquiring that this technical problem should be solved.
[0009]
[Formula 4]



(I)

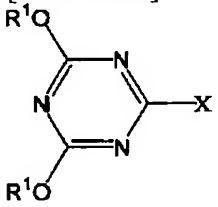
(R1 is the alkyl group of carbon numbers 1-4, or the aryl group of carbon numbers 6-8 among a formula.) R2 is the alkyl group of carbon numbers 1-4, and X is a halogen atom. Without performing the two above staircase reactions using the condensing agent which consists of quarternary ammonium salt shown, by mixing and making this condensing agent, a carboxylic-acid compound, and an amine compound react, yield improves and reaction time can also be shortened, Generating an amide compound by high yield also in a protonic organic solvent unlike the condensing agent of the carbodiimide system which is the general-purpose condensing agent has also found out and proposed these condensing agents in the list at coincidence (Japanese Patent Application No. No. 60765 [11 to]).
[0010] Moreover, when a carboxylic-acid compound and an alcoholic compound are made to react using the same condensing agent as using it in the manufacture approach of the above-mentioned amide compound which this invention person etc. proposed also about manufacture of an ester compound, it has already proposed also about a header and this that an ester compound can be manufactured under mild conditions (Japanese Patent Application No. No. 137693 [11 to]).
[0011]
[Problem(s) to be Solved by the Invention] However, while this invention persons continued to coincidence the examination of a condensation reaction using the quarternary ammonium salt shown by said general formula (I), they became clear [that there is a problem] to this quarternary ammonium salt at stability at it. That is, in the above-mentioned quarternary ammonium salt, it became clear that a decomposition reaction occurs during the manufacture, preservation, or use. In the preservation and handling, it this not only causes the fall of the purity of this quarternary ammonium salt, and decline in condensation yield, but means that it is necessary to pay attention.
[0012] Moreover, the quarternary ammonium salt shown by said general formula (I) can usually be manufactured by making the triazine compound and morpholine compound of structure which correspond, respectively react in an organic solvent. However, by this approach, the unreacted triazine compound was contained in this quarternary ammonium salt that a reaction was not completed even if it carried out the long duration reaction, consequently was manufactured by this approach about 1 to 5%.
[0013] Therefore, this invention aims at offering the approach of manufacturing efficiently this quarternary ammonium salt by which stability has been improved while it offers the approach of raising the stability of the quarternary ammonium salt shown by said general formula (I).
[0014]
[The means for solving invention] this invention persons inquired wholeheartedly that this technical problem should be solved. Consequently, when a triazine compound and a morpholine compound were made to react in the organic solvent containing the water of the amount of specification, it came to

complete header this invention for being hard to decompose and stability of water content quarternary ammonium salt which the hydrated compound containing the quarternary ammonium salt of a high grade is obtained, and is moreover obtained for a short time improving.
[0015] That is, this invention is the following general formula (I).
[0016]
[Formula 5]



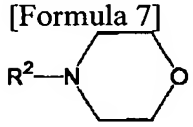
・・・・・・(I)

[0017] (-- R1 is the alkyl group of carbon numbers 1-4, or the aryl group of carbon numbers 6-8 among a formula, R2 is the alkyl group of carbon numbers 1-4, and X is a halogen atom.) -- it is water content quarternary ammonium salt which consists of 60 to quarternary-ammonium-salt 99 mass % shown, and 40 to water 1 mass %.
[0018] Moreover, other invention is the following general formulas (II).
[0019]
[Formula 6]



・・・・・・(II)

[0020] (-- R1 is the alkyl group of carbon numbers 1-4, or the aryl group of carbon numbers 6-8 among a formula, and X is a halogen atom.) -- the triazine compound shown and the following general formula (III)
[0021]
[Formula 7]



・・・・・・(III)

[0022] (-- R2 is the alkyl group of carbon numbers 1-4 among a formula.) -- it is the manufacture approach of the water content quarternary ammonium salt of above-mentioned this invention characterized by making the morpholine compound shown react under 0.1-10-mol existence of water and in an organic solvent to one mol of said triazine compounds.
[0023] In the manufacture approach of above-mentioned this invention, although not restrained by the theory, decomposition of the quarternary ammonium salt generated with it while the reaction was promoted by the moisture which exists in the system of reaction is controlled, and it is thought that the effectiveness of compaction and high-grade-izing of reaction time is discovered.
[0024] The water content quarternary ammonium salt of said this invention can be suitably used as a condensing agent in the method of making for example, a carboxylic-acid compound and an amine compound react, and manufacturing an amide compound, or the method of making a carboxylic-acid compound and an alcoholic compound react, and manufacturing an ester compound.
[0025] the effectiveness which according to the manufacture approach of these carboxylic-acids compound derivative (an amide compound or ester compound) using the condensing agent of this invention is acquired when the condensing agent which is shown in said Japanese-Patent-Application-

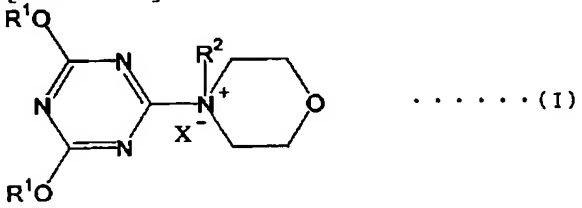
No. No. 60765 [11 to] official report or Japanese-Patent-Application-No. No. 137693 [11 to] official report carried out, and which consists of quarternary ammonium salt shown by said general formula (I) is used -- in addition, decomposition of this quarternary ammonium salt does not take place to reaction time, but improvement in reaction yield is also found.

[0026]

[Embodiment of the Invention] The water content quarternary ammonium salt of this invention is the following general formula (I).

[0027]

[Formula 8]



(I)

[0028] (-- R1 is the alkyl group of carbon numbers 1-4, or the aryl group of carbon numbers 6-8 among a formula, R2 is the alkyl group of carbon numbers 1-4, and X is a halogen atom.) -- the quarternary ammonium salt shown is included.

[0029] R1 in the above-mentioned general formula (I) is the alkyl group of carbon numbers 1-4, or the aryl group of carbon numbers 6-8, and R2 is the alkyl group of carbon numbers 1-4. As an alkyl group of carbon numbers 1-4, a methyl group, an ethyl group, n-propyl group, an isopropyl group, n-butyl, an isobutyl radical, etc. can be mentioned, and a phenyl group, a tolyl group, a xylyl group, etc. can be mentioned as an aryl group of carbon numbers 6-8. Also in these, in the semantics that especially composition is easy, a methyl group and an ethyl group are adopted as an alkyl group, and a phenyl group is suitably adopted as an aryl group.

[0030] Moreover, X in the above-mentioned general formula (I) can show a halogen atom, and can mention a fluorine, chlorine, a bromine, iodine, etc. as a halogen atom. Also in these, chlorine is suitably adopted in the semantics that especially composition is easy.

[0031] If the quarternary ammonium salt shown by the above-mentioned general formula (I) of this invention is illustrated concretely 4-(4, 6-dimethoxy-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-diethoxy-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-dipropoxy-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-JIISO propoxy-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-dibutoxy-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-JIFENOKISHI-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-dimethoxy-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU chloride, 4-(4, 6-diethoxy-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU chloride, 4-(4, 6-dipropoxy-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU chloride, 4-(4, 6-JIISO propoxy-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU chloride, 4-(4, 6-dibutoxy-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU chloride, 4-(4, 6-JIFENOKISHI-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU chloride, 4-(4, 6-dimethoxy-1,3,5-triazine-2-IRU)-4-isobutyl mol HORINIUMU chloride, 4-(4, 6-diethoxy-1,3,5-triazine-2-IRU)-4-isobutyl mol HORINIUMU chloride, 4-(4, 6-dipropoxy-1,3,5-triazine-2-IRU)-4-isobutyl mol HORINIUMU chloride, 4-(4, 6-JIISO propoxy-1,3,5-triazine-2-IRU)-4-isobutyl mol HORINIUMU chloride, 4-(4, 6-dibutoxy-1,3,5-triazine-2-IRU)-4-isobutyl mol HORINIUMU chloride, 4-(4, 6-JIFENOKISHI-1,3,5-triazine-2-IRU)-4-isobutyl mol HORINIUMU chloride, etc. can be mentioned.

[0032] Condensation yield high [composition is easy also especially in these, and] when it is moreover used as a condensing agent is expectable. 4-(4, 6-dimethoxy-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-diethoxy-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-dipropoxy-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-JIFENOKISHI-1,3,5-triazine-2-IRU)-4-methyl mol HORINIUMU chloride, 4-(4, 6-dimethoxy-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU chloride, 4-(4, 6-diethoxy-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU

chloride, 4-(4, 6-dipropoxy-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU chloride, 4-(4, 6-JIFENOKISHI-1,3,5-triazine-2-IRU)-4-ethyl mol HORINIUMU chloride, etc. are adopted especially suitably.

[0033] In this invention, it is indispensable to make the quarternary ammonium salt shown by the above-mentioned general formula (I) contain the water of 40 - 1 mass % on the basis of the sum total mass of the quarternary ammonium salt concerned and water.

[0034] When the content of water is under 1 mass %, sufficient effectiveness to control decomposition of quarternary ammonium salt and raise stability is not acquired. Moreover, if the content of water exceeds 40 mass %, the condition of water content quarternary ammonium salt will be in a semisolid condition, handling not only becomes complicated, but hydrolysis will take place and stability will fall on the contrary. It is suitable for the moisture content in the water content quarternary ammonium salt of the viewpoint of the handling nature of quarternary ammonium salt, and stability to this invention that it is 35 to 3 mass %. Measurement of moisture content can perform measurement using measurement, a curl Fischer moisture meter, etc. which used the thermobalance etc. with the usual moisture content measuring method.

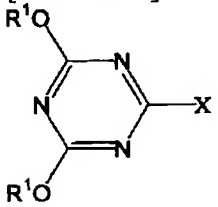
[0035] In addition, in the water content quarternary ammonium salt of this invention, especially a water's existence gestalt is not limited, but even if contained in the form of water of crystallization, it may be included in the form of free water.

[0036] Although especially the manufacture approach of the water content quarternary ammonium salt of this invention is not limited, it can be suitably manufactured, for example by the following approaches (the manufacture approach of this invention).

[0037] Namely, the following general formula (II)

[0038]

[Formula 9]

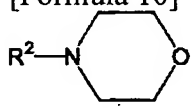


. . . . . (II)

[0039] (-- R1 is the alkyl group of carbon numbers 1-4, or the aryl group of carbon numbers 6-8 among a formula, and X is a halogen atom.) -- the triazine compound shown and the following general formula (III)

[0040]

[Formula 10]



. . . . . (III)

[0041] (-- R2 is the alkyl group of carbon numbers 1-4 among a formula.) -- it can obtain suitably by making the morpholine compound shown react under 0.1-10-mol existence of water and in an organic solvent to one mol of said triazine compounds.

[0042] If the triazine derivative shown by the above-mentioned general formula (II) is illustrated concretely 2-chloro -4, 6-dimethoxy-1,3,5-triazine, 2-chloro -4, 6-diethoxy-1,3,5-triazine, 2-chloro -4, 6-JIPUROKISHI-1,3,5-triazine, 2-chloro -4, 6-JIISO proxy-1,3,5-triazine, 2-chloro -4, 6-G n-butoxy-1,3,5-triazine, 2-chloro -4, 6-JIISO butoxy-1,3,5-triazine, 2-chloro -4, and 6-JIFENOKISHI-1,3,5-triazine can be mentioned. Also in these, 2-chloro -4 especially with easy composition, 6-dimethoxy-1,3,5-triazine, 2-chloro -4, 6-diethoxy-1,3,5-triazine, 2-chloro -4, 6-dipropoxy-1,3,5-triazine, 2-chloro -4, and 6-JIFENOKISHI-1,3,5-triazine are adopted especially suitably.

[0043] Although these triazine derivatives also have a thing available as an industrial raw material, it is

acquirable by making cyanuric chloride and corresponding alcohol react to the bottom of sodium-hydrogencarbonate existence generally.
[0044] As a morpholine compound shown by the above-mentioned general formula (III), 4-methyl morpholine, 4-ethyl morpholine, 4-isobutyl morpholine, etc. can be mentioned. these morpholine compounds -- all -- as a reagent and an industrial raw material -- acquisition -- it is easy.
[0045] In the manufacture approach of this invention, although especially the amount of the morpholine compound used shown by the above-mentioned general formula (III) is not limited, one mol of these compounds reacts to one mol of triazine compounds usually shown by the above-mentioned general formula (II). In such an equimolar reaction, in order to make the invert ratio of one of raw material compounds into 100%, it is common to use either for an excess a little, and it is suitable also in the manufacture approach of this invention to use [0.7-1.3, especially 0.8-1.2 mols] the morpholine compound shown by the above-mentioned general formula (III) to one mol of triazine compounds shown by the above-mentioned general formula (II).
[0046] If it is the organic solvent which does not check a reaction as an organic solvent, it can use that there is no limit in any way. When the organic solvent used for this reaction is illustrated concretely, a tetrahydro furan, Ether, such as 1,4-dioxane, diethylether, and diisopropyl ether, Halogenated aliphatic hydrocarbon, such as a methylene chloride, chloroform, and a carbon tetrachloride Ester, such as ethyl acetate and propyl acetate, an acetone, a methyl ethyl ketone, Nitril, such as ketones, such as methyl isobutyl ketone, an acetonitrile, and propionitrile Aromatic hydrocarbon, such as benzene, toluene, and a xylene, a chlorobenzene, Halogenated-aromatics hydrocarbons, such as a dichlorobenzene, N.N-dimethylformamide, Those, such as alcohols, such as carbonate, such as aliphatic hydrocarbon, such as amides, such as N,N-dimethylacetamide, a hexane, and a heptane, and dimethyl carbonate, t-butyl alcohol, and t-amyl alcohol, and dimethyl sulfoxide, can be mentioned. Organic solvents, such as carbonate, such as aromatic hydrocarbon, such as nitril, such as ketones, such as ester, such as ether, such as the tetrahydrofuran and 1,4-dioxane which can expect high isolation yield especially also in these, diethylether, and diisopropyl ether, a methylene chloride, halogenated aliphatic hydrocarbon of chloroform, ethyl acetate, and propyl acetate, an acetone, a methyl ethyl ketone, and methyl isobutyl ketone, an acetonitrile, and propionitrile, benzene, toluene, and a xylene, and dimethyl carbonate, are adopted suitably.
[0047] Although there is especially no limit as amount of the organic solvent used in the manufacture approach of this invention, if there are not much many amounts, the yield per one batch falls and is not economical, and if there are not much few amounts, in order to cause trouble to stirring etc., it is good 0.1 - 60 mass % and for the concentration of the quarternary ammonium salt shown by the usually generated above-mentioned general formula (I) to choose so that it may become 1 - 50 mass % preferably.
[0048] In the manufacture approach of this invention, in order that the quarternary ammonium salt of a high grade may be included and moisture content may obtain easily the water content quarternary ammonium salt of a predetermined value for a short time, it is important to make 0.1-10-mol water exist in performing the reaction of said triazine compound and said morpholine compound to one mol of said triazine compounds in an organic solvent.
[0049] If the amount of the water which makes reaction time live together separates from the above-mentioned range and there are, sufficient effectiveness to control decomposition of this quarternary ammonium salt that happens during a reaction will not be acquired, but if many [conversely / too], yield will fall. [too few] It is suitable for the amount of the water made to live together from a viewpoint of effectiveness (the reaction-time compaction effectiveness and high-grade-izing) that it is especially 0.2-8 mols to one mol of said triazine compounds.
[0050] The reaction of said triazine compound in the manufacture approach of this invention and said morpholine compound can be performed by contacting both in the organic solvent containing the water of the specified quantity. Stirring is suitable in order to react to homogeneity for a short time. Moreover, when the compound and product which are usually used although it can carry out under atmospheric air have hygroscopicity, as for a reaction, it is desirable to carry out under inert gas ambient atmospheres,

such as dry air which let dry pipes, such as calcium chloride tubing, pass or nitrogen, helium, and an argon. This reaction can be carried out also in the state of any of reduced pressure, ordinary pressure, and pressurization.

[0051] Although there is especially no limit as reaction temperature of the above-mentioned reaction, if a reaction rate will become small if temperature is not much low, and temperature is not much high, in order to promote side reaction, it is usually good to choose [-20-70-degree C] from the range of -10-60 degrees C preferably. Moreover, it is enough if especially a limit usually has ** as reaction time as long as 0.1 to 10 hours.

[0052] Thus, since it usually deposits as a crystal, the quarternary ammonium salt shown by the generated above-mentioned general formula (I) is acquirable by drying by the usual desiccation approaches, such as ventilation desiccation and reduced pressure drying, after separating a solid-state by the usual solid-liquid-separation approaches, such as centrifugal separation, centrifugal filtration, an expression, and filtration under reduced pressure. Under the present circumstances, what is necessary is just to adjust the water content made into the purpose by adjusting desiccation conditions. Moreover, a water content may be adjusted by mixing water further to the acquired water content quarternary ammonium salt.

[0053] Moreover, when a crystal does not deposit, after removing the used organic solvent as much as possible, solvents, such as a tetrahydro furan, are added, and it considers as a slurry regime, and can acquire by the above-mentioned approach.

[0054] The water content quarternary ammonium salt of this invention can be suitably used as a condensing agent at the time of making a carboxylic-acid compound and an alcoholic compound react, and manufacturing an ester compound, in case a carboxylic-acid compound and an amine compound are made to react and an amide compound is manufactured like the quarternary ammonium salt shown by the conventional general formula (I). Under the present circumstances, decomposition of the quarternary ammonium salt under condensation reaction is not only controlled, but although based also on the system of reaction, yield improves about several% rather than the case where the quarternary ammonium salt which does not contain water is used.

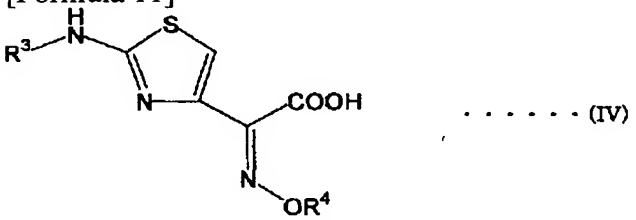
[0055] Hereafter, how to manufacture these compounds, using the water content quarternary ammonium salt of this invention as a condensing agent is explained.

[0056] (1) Explanation about the approach (henceforth the amide manufacture approach of this invention) of making a carboxylic-acid compound and an amine compound reacting, and manufacturing an amide compound, using the water content quarternary ammonium salt of this invention as a condensing agent.

[0057] The amide manufacture approach of this invention can be performed like the approach of using the conventional condensing agent, except using the water content quarternary ammonium salt of this invention as a condensing agent. For example, the water content quarternary ammonium salt and the carboxylic-acid compound of this invention are made to react beforehand, without making it react with an amine compound and making such a reactant derivative form beforehand, after making the reactant derivative which is intermediate field form, it may mix and the three above-mentioned kinds of reaction agents may be made to react. However, it is suitable to adopt the latter approach to which mix and three kinds of reaction agents are made to react from viewpoints, such as height of reaction yield and shortness of reaction time.

[0058] What is necessary is not to limit the class of water content quarternary ammonium salt used as a condensing agent in this invention, and especially its amount used, but just to determine them suitably according to the system of reaction. Although each water content quarternary ammonium salt of this invention is usable to this manufacture approach, it is suitable 60 to quarternary-ammonium-salt 99 mass % which carried out the above-shown indication as what can expect condensation yield high [composition is easy especially, and] when it is moreover used as a condensing agent, and to use especially 65 to 97 mass % and 40 to water 1 mass %, and the thing that consists of 35 to 3 mass % especially. Moreover, since there is an inclination for a condensation reaction to finish incomplete generally if there is not much little amount of the condensing agent used, and to react with an amine

compound if there are not much many amounts, and for yield to fall about the amount used, it is suitable to carry out [from which 0.9-1.3 mols of quarternary ammonium salt become 0.95-1.2 mols especially to one mol of carboxylic-acid compounds] amount use.
[0059] Next, the carboxylic-acid compound used by the amide manufacture approach of this invention is explained.
[0060] If it is the compound which has the carboxyl group as a carboxylic-acid compound used in this invention, it can be used that there is no limit in any way.
[0061] When these compounds are illustrated concretely, acetic-acid, propionic-acid, 2, and 2-dimethyl propionic acid, Butanoic acid, pentanoic acid, a hexanoic acid, oenanthic acid, an octanoic acid, nonoic acid, Aliphatic-carboxylic-acid compounds, such as a decanoic acid, undecanoic acid, an acrylic acid, and a methacrylic acid; A benzoic acid, o-nitro benzoic acid, m-nitro benzoic acid, p-nitrobenzoic acid, o-chlorobenzoic acid, m-chloro benzoic acid, para chlorobenzoic acid, o-methoxy benzoic acid, m-methoxy benzoic acid, para methoxy benzoic acid, 3-phenyl propionic acid, Aromatic-carboxylic-acid compound; 2-aminothiazole acetic-acid derivatives, such as 3-phenyl-2-propenoic acid, 2-(4-methoxypheny) acetic acid, and 3-(4-hydroxyphenyl) propionic acid; the amino acid derivative from which the amino group was protected can be mentioned.
[0062] In order to obtain a cephem system compound as an amide compound in this invention, it is the following general formula (IV) as a carboxylic-acid compound.
[0063]
[Formula 11]



. . . . . (IV)

[0064] (-- R3 is a hydrogen atom, an acyl group, an alkoxy carbonyl group, an aralkyloxy carbonyl group, or an aralkyl radical among a formula, and R4 is a hydrogen atom, an alkyl group, an aralkyl radical, an acyl group, or an alkoxy carbonyl alkyl group.) -- it is suitable to use a 2-aminothiazole acetic-acid derivative as shown.
[0065] Here, a cephem system compound means the compound which generally has a SEFAROSUPORAN acid in the intramolecular, and when the amine compound which consists of a carboxylic-acid compound which consists of the above 2-aminothiazole acetic-acid derivatives, and a 7-aminocephalosporanic acid derivative mentioned later is made to react, the cephem system compound which has the structure corresponding to each use raw material as an amide compound can be manufactured.
[0066] as the acyl group shown by R3 in the above-mentioned general formula (IV), an alkoxy carbonyl group, an aralkyloxy carbonyl group, and an aralkyl radical -- desorption -- if it is an easy radical, it can be used that there is no limit in any way. When a suitable radical is concretely explained among these radicals, as an acyl group The radical of the carbon numbers 1-5, such as a formyl group, an acetyl group, a butyryl radical, an isobutyryl radical, a valeryl radical, and a pivaloyl radical, as a; alkoxy carbonyl group A methoxycarbonyl group, an ethoxycarbonyl radical, a propoxy carbonyl group, The radical of the carbon numbers 2-7, such as an isopropoxycarbonyl radical, a tert-butoxycarbonyl radical, and a tert-amyloxy carbonyl group, as a; aralkyloxy carbonyl group The radical of the carbon numbers 8-10, such as a benzyloxycarbonyl radical and a FENI chill oxy-carbonyl group, is mentioned. Moreover, as an aralkyl radical, the radical of the carbon numbers 7-20, such as benzyl, a diphenyl methyl group, and a triphenylmethyl radical, is suitable.
[0067] Also in these, especially, as an acyl group, a methoxycarbonyl group or a tert-butoxycarbonyl radical is used as an alkoxy carbonyl group, and a benzyloxycarbonyl radical is used for a formyl group

or an acetyl group especially suitably [benzyl or a triphenylmethyl radical] as an aralkyl radical as an aralkyloxy carbonyl group from a viewpoint that the ease and condensation yield of an elimination reaction are high.

[0068] Moreover, the radical which has the effectiveness which discovers drug effect as a cephem compound as the alkyl group shown by R4, an aralkyl radical, an acyl group, or an alkoxy carbonyl alkyl group, or a hydrocarbon group with easy desorption is used that there is no limit in any way. When these suitable are illustrated concretely, as an alkyl group A methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, The low-grade alkyl group of the carbon numbers 1-4, such as tert-butyl, as a; aralkyl radical Benzyl, The radical of the carbon numbers 7-20, such as a diphenyl methyl group and a triphenylmethyl radical, as a; acyl group The radical of the carbon numbers 1-5, such as a formyl group, an acetyl group, a butyryl radical, an isobutyryl radical, a valeryl radical, and a pivaloyl radical, as a; alkoxy carbonyl alkyl group The radical of the carbon numbers 3-8, such as a methoxy carbonylmethyl radical, a 1-methoxycarbonyl-1-methylethyl radical, a tert-butoxy carbonylmethyl radical, and a 1-tert-butoxycarbonyl-1-methylethyl radical, is mentioned. Especially, the alkyl group of the carbon numbers 1-3, such as a methyl group with little steric hindrance, an ethyl group, and a propyl group, is adopted suitably.

[0069] In manufacturing a cephem system compound, also in the 2-aminothiazole acetic-acid derivative shown by said general formula (IV) From a viewpoint that high drug effect can be expected when it changes into a SEEMU system compound R3 A hydrogen atom, a benzyloxycarbonyl radical, a tert-butoxycarbonyl radical, They are a methoxycarbonyl group, a formyl group, a trityl radical, an acetyl group, or a chloro acetyl group. It is suitable to use that whose R4 is a hydrogen atom, a methyl group, an ethyl group, a methoxy carbonylmethyl radical, a 1-methoxycarbonyl-1-methylethyl radical, or benzyl.

[0070] If the 2-aminothiazole acetic-acid derivative shown by said general formula (IV) which can be used suitably is illustrated concretely A 2-(2-aminothiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-formylamino thiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-trityl aminothiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-acetylamino thiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-chloro acetylamino thiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-aminothiazole-4-IRU)-2-hydroxy imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-hydroxy imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-hydroxy imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-hydroxy imino acetic acid, A 2-(2-formylamino thiazole-4-IRU)-2-hydroxy imino acetic acid, A 2-(2-trityl aminothiazole-4-IRU)-2-hydroxy imino acetic acid, A 2-(2-acetylamino thiazole-4-IRU)-2-hydroxy imino acetic acid, A 2-(2-aminothiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-formylamino thiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-trityl aminothiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-acetylamino thiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-chloro acetylamino thiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-aminothiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-formylamino thiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-trityl aminothiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-acetylamino thiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-aminothiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-tert-butoxycarbonyl

aminothiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-formylamino thiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-trityl aminothiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-acetylamino thiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-aminothiazole-4-IRU)-2-ethoxy imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-ethoxy imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-ethoxy imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-ethoxy imino acetic acid, A 2-(2-formylamino thiazole-4-IRU)-2-ethoxy imino acetic acid, A 2-(2-trityl aminothiazole-4-IRU)-2-ethoxy imino acetic acid, A 2-(2-acetylamino thiazole-4-IRU)-2-ethoxy imino acetic acid, a 2-(2-chloro acetylamino thiazole-4-IRU)-2-ethoxy imino acetic acid, etc. can be mentioned.

[0071] A 2-(2-aminothiazole-4-IRU)-2-methoxy imino acetic acid since high condensation yield is expectable also in these, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-formylamino thiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-trityl aminothiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-acetylamino thiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-chloro acetylamino thiazole-4-IRU)-2-methoxy imino acetic acid, A 2-(2-aminothiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-formylamino thiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-acetylamino thiazole-4-IRU)-2-methoxycarbonyl methoxy imino acetic acid, A 2-(2-aminothiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-(1-methoxycarbonyl-1-methylethoxy) imino acetic acid, 2-(2-formylamino thiazole-4-IRU)-2- (a 1-methoxycarbonyl-1-methylethoxy imino acetic acid --) 2-(2-acetylamino thiazole-4-IRU)-2- (a 1-methoxycarbonyl-1-methylethoxy imino acetic acid --) A 2-(2-aminothiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-formylamino thiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-acetylamino thiazole-4-IRU)-2-benzyloxy imino acetic acid, A 2-(2-aminothiazole-4-IRU)-2-ethoxy imino acetic acid, A 2-(2-benzyloxycarbonyl aminothiazole-4-IRU)-2-ethoxy imino acetic acid, A 2-(2-tert-butoxycarbonyl aminothiazole-4-IRU)-2-ethoxy imino acetic acid, A 2-(2-methoxycarbonyl aminothiazole-4-IRU)-2-ethoxy imino acetic acid, It is suitable especially to use a 2-(2-formylamino thiazole-4-IRU)-2-ethoxy imino acetic acid, a 2-(2-acetylamino thiazole-4-IRU)-2-ethoxy imino acetic acid, etc.

[0072] in addition, among the 2-aminothiazole acetic-acid derivatives shown by the above-mentioned general formula (IV), about an oxy-imino group, it is theoretically alike and the Singh (Z) object and both the isomers of an anti-(E) object exist. Although it is both usable in this invention, since pharmacological activity with the more expensive Singh object is expected when using it to a 7-aminocephalosporanic acid derivative, the Singh object is used preferably.

[0073] These 2-aminothiazole acetic-acid derivatives are easily compoundable from an available raw material industrially. As a reagent, for example, or the 2-(2-aminothiazole-4-IRU)-2-methoxyimino ethyl acetate which can come to hand as an industrial raw material, 2-(2-aminothiazole-4-IRU)-2-hydroxy imino ethyl acetate, 2-(2-aminothiazole-4-IRU)-2- (1-methoxycarbonyl-1-methylethoxy imino ethyl acetate --) 2-aminothiazole acetic-ester compounds, such as 2-(2-aminothiazole-4-IRU)-2-methoxycarbonyl methoxyimino ethyl acetate, are used as a start raw material. To this as occasion demands Acetyl chloride, chloro acetyl chloride, a trityl chloride, If still more nearly required after making amino-group protective agents, such as benzyloxycarbonyl chloride, methoxycarbonyl chloride, G tert-butyl dicarbonate, formic acid methyl, and formic acid ethyl, act and protecting the amino group

It is possible to manufacture by hydrolyzing by protecting a hydroxyimino group using the protective agent of hydroxyl groups, such as a dimethyl sulfate, a diethyl sulfate, benzyl chloride, and a benzyl star's picture.

[0074] Moreover, when it is going to obtain the peptide compound which is a compound very important as a physic intermediate product by the amide manufacture approach of this invention, it is suitable to use the amino acid compound derivative from which the amino group was protected as a carboxylic-acid compound.

[0075] In addition, generally a peptide compound says the compound which has two or more amino acid to the intramolecular, the amino acid compound derivative from which the amino group was protected as a carboxylic-acid compound is used, and when the amino acid compound derivative from which the carboxyl group later mentioned as an amine compound was protected is used, the peptide compound which has the structure corresponding to each use raw material as an amide compound can be manufactured.

[0076] Here, although it can use that there is no limit in any way if it is the compound from which it has an amino group and a carboxyl group in intramolecular, and the amino group was protected by the protective group as an amino acid compound derivative from which the amino group was protected, the compound from which the amino group of available amino acid was generally easily protected as an industrial raw material as a reagent is used.

[0077] Here, the above-mentioned protective groups are a formyl group, an acetyl group, benzoyl, a benzyloxycarbonyl radical, a tert-butoxycarbonyl radical, an allyloxy carbonyl group, a methoxycarbonyl group, a trityl radical, a fluorenyl methoxycarbonyl group, etc.

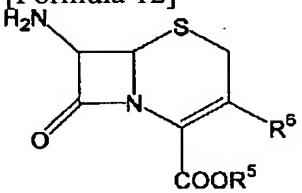
[0078] If the amino acid compound derivative from which the amino group which can be used suitably because of peptide compound manufacture was protected is illustrated concretely alpha-amino butanoic acid, alpha-methyl alanine, an alanine, N-methyl alanine, The beta-alanine, gamma-amino butanoic acid, 5-amino pentanoic acid, 6-amino hexanoic acid, 7-amino hexanoic acid, 8-amino octanoic acid, 11-amino undecanoic acid, 12-amino undecanoic acid, an arginine, an asparagine, an aspartic acid, beta-cyclohexyl alanine, a cyclohexyl glycine, S-acetamide cysteine, A S-tert-butyl cysteine, S-ethyl thiocysteine, a S-p-methoxybenzyl cysteine, S-trityl cysteine, a S-p-methylbenzyl homocysteine, A glutamine, an N-gamma-ethyl glutamine, a N-gamma-trityl glutamine, Glutamic acid, isoglutamine, a glycine, N-methyl glycine, a histidine, pi-benzyloxy methylhistidine, 1-methyl histidine, 3-methyl histidine, An isoleucine, a leucine, N-methyl leucine, a lysine, a N-epsilon-acetyl lysine, A N-epsilon-formyl leucine, a N-epsilon-benzyloxycarbonyl leucine, A methionine, a norleucine, a norvaline, an ornithine, 4-benzoyl FANIRU alanine, A FANIRU alanine, 4-chlorophenyl alanine, 4-fluoro phenylalanine, 4-benzyloxycarbonylamino phenylalanine, a gay phenylalanine, Phenylglycine, 4-hydroxy phenylglycine, a proline, a homoproline, 4-hydroxyproline, O-benzyl hydroxyproline, N-methyl glycine, Homoserine, O-benzyl homoserine, O-benzyl serine, a serine, The compound which protected amino groups, such as a tert-butyl serine, O-methyl serine, threonine, O-benzyl threonine, a tryptophan, a thyrosin, an O-tert-butyl thyrosin, O-benzyl thyrosin, and a valine, by said protective group can be mentioned.

[0079] Although there is not little what has asymmetrical carbon in the above-mentioned amino acid, in this invention, L bodies, D objects, and those mixture can be used that there is no limit in any way.

[0080] Although these compounds are usually available as a reagent and an industrial raw material When acquisition is difficult, the above-mentioned amino acid The inside of an organic solvent, a methyl morpholine, Formic acid methyl, formic acid ethyl after adding the third class amines, such as triethylamine, Acetyl chloride, an acetic anhydride, benzoyl chloride, benzyloxycarbonyl chloride, G tert-butoxycarbonyl dicarbonate and a G tert-butoxycarbonyl full ora -- the id -- After protecting using the protective agent of amino groups, such as diaryl oxy-carbonyl dicarbonate, methoxycarbonyl chloride, a trityl chloride, and fluorenyl methoxycarbonyl chloride, it can manufacture by neutralization and crystallization.

[0081] Next, the amine compound used by the amide manufacture approach of this invention is explained.

[0082] As an amine compound used by this invention, the compound which has the amino group of the first class or the second class can use it that there is no limit in any way.
[0083] When the amine compound used for this invention is illustrated concretely, ethylamine, 1-propylamine, isopropylamine, 1-butylamine, an isobutyl amine, A sec-butylamine, 1, 2-dimethyl propylamine, a tert-butylamine, 1-pentylamine, 1-hexylamine, 2-ethylhexylamine, 1-heptyl amine, 1-octyl amine, 1-nonyl amine, 1-deca nil amine, 1-undecanyl amine, dimethylamine, diethylamine, diisopropylamine, Allylamine, a diaryl amine, a pyrrolidine, a 3-hydroxy pyrrolidine, A piperidine, 2-pipecoline, 3-PIPEKORIN, 4-pipecoline, 2, 4-RUPECHIJIN, 2, 6-RUPECHIJIN, 3, 5-RUPECHIJIN, N-methyl gay piperazine, N-acyl gay piperazine, N-methyl piperazine, N-ethoxycarbonyl piperazine, p-chlorophenyl piperazine, 1-(2-pyrimidyl) piperazine, A 1-amino-4-cyclohexyl piperazine, 1-cyclohexyl piperazine, 3-hydroxymethyl piperidine, N-amino piperidine, N-AMINOPIPEKORIN, 2-hydroxyethyl piperidine, hydroxy ethylamine, 3-hydroxy propylamine, 2-hydroxy propylamine, 1-hydroxy-2-propylamine, 3-methoxypropylamine, 3-ethoxypropylamine, 3-butoxy propylamine, 3-(2-ethylhexyloxy) propylamine, 3-DESHIROKISHI propylamine, 3-RAUROKISHI propylamine, 3-millimeter SUCHIROKISHI propylamine, Dimethyl AMINI ethylamine, diethylamino ethylamine, dimethylamino propylamine, Dibutylaminopropylamine, dimethylamino ethoxy propylamine, Fatty amine compounds, such as a methoxy amine; An aniline, benzylamine, Dibenzylamine, alpha-phenethylamine, beta-phenethylamine, 2-aminothiazole, 2-aminopyridine, 3-aminopyridine, 4-aminopyridine, Indore, N-(2-pyridyl) piperazine, A furfuryl amine, 2-amino pyrazine, 2-amino-5-methylpyridine, Aromatic amine compounds, such as 2-amino-6-methylpyridine, the 2-amino -4, and 6-lutidine; the amino acid derivative from which 7-aminocephalosporanic acid derivative; and a carboxyl group were protected can be mentioned.
[0084] As mentioned above, in order to obtain a cephem compound, it is suitable also in these amines compound to use a 7-aminocephalosporanic acid derivative. As a 7-aminocephalosporanic acid derivative which can be used suitably, it is the following general formula (V).
[0085]
[Formula 12]



. . . . . (V)

[0086] The inside of {type, R5 alkyl group, an aralkyl radical, an aryl group, an alkoxy carbonyl alkyl group, An alkoxy KARUBONI oxy-alkyl group, an alkylcarbonyloxy alkyl group, It is a trialkylsilyl group. R6 Or a hydrogen atom, a methoxymethyl radical, A chlorine atom, an iodine methyl group, a vinyl group, an acetyl oxymethyl radical, 2-FURARU carbonyl thiomethyl radical, A thiomethyl radical, a thiomethyl (1-methyl tetrazole-5-IRU) radical, (1, 2, 3-thiadiazole-5-IRU) (5-methyl tetrazole-3-IRU) They are a methyl group, a (Z)-2-(1, 2, 3-thiadiazole-4-IRU) ethenyl radical, a (Z)-2-(4-methyl thiazole-5-IRU) ethenyl radical, or (1H- 1, 2, 3-triazole-5-IRU) a thiomethyl thio radical. The compound shown by} can be mentioned.
[0087] As the alkyl group shown by R5, an aralkyl radical, an aryl group, an alkoxy carbonyl alkyl group, an alkoxycarbonyloxyalkyl group, an alkylcarbonyloxy alkyl group, or a trialkylsilyl group, a radical with easy hydrolysis is used among the above-mentioned general formula (V) that there is no limit in any way. When these suitable are illustrated concretely, as an alkyl group A methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, The low-grade alkyl group of the carbon numbers 1-4, such as tert-butyl, as a; aralkyl radical Benzyl, The radical of the carbon numbers 7-20, such as a diphenyl methyl group and a triphenylmethyl radical, as a; aryl group The radical of the carbon numbers 6-8, such as a phenyl group and a tolyl group, as a; alkoxy carbonyl alkyl group A methoxy carbonylmethyl radical, a 1-methoxycarbonyl-1-methylethyl radical, and a tert-butoxy

carbonylmethyl radical as a; alkoxycarbonyloxyalkyl group A 1-tert-buthoxycarbonyloxy ethyl group, 1-cyclohexyloxycarbonyloxyethyl radical, The radical of the carbon numbers 3-10, such as 1-ethoxycarbonyloxy ethyl group, as a; alkylcarbonyloxy alkyl group The radical of the carbon numbers 3-10, such as a methyl carbonyloxy methyl group, an ethyl carbonyloxy methyl group, and a tert-butyl carbonyloxy methyl group, as a; trialkylsilyl group The radical of the carbon numbers 3-9, such as a trimethylsilyl radical, a triethyl silyl radical, and a tert-butyldimethylsilyl radical, is mentioned.
[0088] From a viewpoint that hydrolysis is easy, as an alkyl group chemically or physiologically especially also in these radicals A methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, The low-grade alkyl group of the carbon numbers 1-4, such as tert-butyl, as a; alkoxy carbonyl alkyl group A methoxy carbonylmethyl radical, a 1-methoxycarbonyl-1-methylethyl radical, and a tert-butoxy carbonylmethyl radical as a; alkoxycarbonyloxyalkyl group A 1-tert-buthoxycarbonyloxy ethyl group, 1-cyclohexyl carbonyloxy ethyl group, It is suitable especially to use the radical of the carbon numbers 3-9, such as a trimethylsilyl radical, a triethyl silyl radical, and t-butyldimethylsilyl radical, for the radical of the carbon numbers 3-10, such as 1-ethoxycarbonyloxy ethyl group, as a; trialkylsilyl group.
[0089] If the 7-aminocephalosporanic acid derivative shown by the above-mentioned general formula (V) used suitably is illustrated concretely 7-amino-3-cephem-4-carboxylic-acid methyl, 7-amino - 3-chloro-3-cephem-4-carboxylic-acid methyl, 7-amino-3-iodine methyl-3-cephem-4-carboxylic-acid methyl, 7-amino - 3-vinyl-3-cephem-4-carboxylic-acid methyl, 7-amino-3-acetyl oxymethyl-3-cephem-4-carboxylic-acid methyl, 7-amino-3-(2-FURARU carbonyl thiomethyl)-3-cephem-4-carboxylic-acid methyl, 7-amino - 3-[(1, 2, 3-thiadiazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid methyl, 7-amino - 3-[(1-methyl tetrazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid methyl, 7-amino - 3-[(Z)-2-(1, 2, 3-thiadiazole-4-IRU) ethenyl]-3-cephem-4-carboxylic-acid methyl, 7-amino - 3-[(5-methyl tetrazole-3-IRU) methyl]-3-cephem-4-carboxylic-acid methyl, 7-amino - 3-[(Z)-2-(4-methyl thiazole-5-IRU) ethenyl]-3-cephem-4-carboxylic-acid methyl, 7-amino - 3-[(1H- 1, 2, 3-triazole-5-IRU) thiomethyl thio]-3-cephem-4-carboxylic-acid methyl, 7-amino-3-cephem-4-carboxylic-acid ethyl, 7-amino - 3-chloro-3-cephem-4-carboxylic-acid ethyl, 7-amino-3-iodine methyl-3-cephem-4-carboxylic-acid ethyl, 7-amino - 3-vinyl-3-cephem-4-carboxylic-acid ethyl, 7-amino-3-acetyl oxymethyl-3-cephem-4-carboxylic-acid ethyl, 7-amino-3-(2-FURARU carbonyl thiomethyl)-3-cephem-4-carboxylic-acid ethyl, 7-amino - 3-[(1, 2, 3-thiadiazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid ethyl, 7-amino - 3-[(1-methyl tetrazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid ethyl, 7-amino - 3-[(Z)-2-(1, 2, 3-thiadiazole-4-IRU) ethenyl]-3-cephem-4-carboxylic-acid ethyl, 7-amino - 3-[(5-methyl tetrazole-3-IRU) methyl]-3-cephem-4-carboxylic-acid ethyl, 7-amino - 3-[(Z)-2-(4-methyl thiazole-5-IRU) ethenyl]-3-cephem-4-carboxylic-acid ethyl, 7-amino - 3-[(1H- 1, 2, 3-triazole-5-IRU) thiomethyl thio]-3-cephem-4-carboxylic-acid ethyl, 7-amino-3-cephem-4-carboxylic-acid isopropyl, 7-amino - 3-chloro-3-cephem-4-carboxylic-acid isopropyl, 7-amino-3-iodine methyl-3-cephem-4-carboxylic-acid isopropyl, 7-amino - 3-vinyl-3-cephem-4-carboxylic-acid isopropyl, 7-amino-3-acetyl oxymethyl-3-cephem-4-carboxylic-acid isopropyl, 7-amino-3-(2-FURARU carbonyl thiomethyl)-3-cephem-4-carboxylic-acid isopropyl, 7-amino - 3-[(1, 2, 3-thiadiazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid isopropyl, 7-amino - 3-[(1-methyl tetrazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid isopropyl, 7-amino - 3-[(Z)-2-(1, 2, 3-thiadiazole-4-IRU) ethenyl]-3-cephem-4-carboxylic-acid isopropyl, 7-amino - 3-[(5-methyl tetrazole-3-IRU) methyl]-3-cephem-4-carboxylic-acid isopropyl, 7-amino - 3-[(Z)-2-(4-methyl thiazole-5-IRU) ethenyl]-3-cephem-4-carboxylic-acid isopropyl, 7-amino - 3-[(1H- 1, 2, 3-triazole-5-IRU) thiomethyl thio]-3-cephem-4-carboxylic-acid isopropyl, 7 - Amino-3-cephem-4-carboxylic-acid tert-butyl, 7-amino -3 - Chloro-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-3-iodine methyl-3-cephem-4-carboxylic-acid tert-butyl, 7-amino -3 - Vinyl-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-3-acetyl oxymethyl-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-3-(2-FURARU carbonyl thiomethyl)-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-3-[(1, 2, 3-thiadiazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-3-[(1-methyl tetrazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-3-[(Z)-2-(1, 2, 3-thiadiazole-4-IRU) ethenyl]-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-3-[(5-methyl tetrazole-3-IRU) methyl]-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-

3-[(Z)-2-(4-methyl thiazole-5-IRU) ethenyl]-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-3-[(1H- 1, 2, 3-triazole-5-IRU) thiomethyl thio]-3-cephem-4-carboxylic-acid tert-butyl, 7-amino-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-chloro-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino -3 - Iodine methyl-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-vinyl-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino -3 - Acetyl oxymethyl-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-(2-FURARU carbonyl thiomethyl)-3-cephem - 4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-[(1, 2, 3-thiadiazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-[(1-methyl tetrazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-[(Z)-2-(1, 2, 3-thiadiazole-4-IRU) ethenyl]-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-[(5-methyl tetrazole-3-IRU) methyl]-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-[(Z)-2-(4-methyl thiazole-5-IRU) ethenyl]-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-[(1H- 1, 2, 3-triazole-5-IRU) thiomethyl thio]-3-cephem-4-carboxylic-acid methoxy carbonylmethyl, 7-amino-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-chloro-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino -3 - Iodine methyl-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-vinyl-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino -3 - Acetyl oxymethyl-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-(2-FURARU carbonyl thiomethyl)-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-[(1, 2, 3-thiadiazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-[(1-methyl tetrazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-[(Z)-2-(1, 2, 3-thiadiazole-4-IRU) ethenyl]-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-[(5-methyl tetrazole-3-IRU) methyl]-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-[(Z)-2-(4-methyl thiazole-5-IRU) ethenyl]-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-[(1H- 1, 2, 3-triazole-5-IRU) thiomethyl thio]-3-cephem-4-carboxylic-acid diphenyl methyl, 7-amino-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino - 3-chloro-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino-3-iodine methyl-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino - 3-vinyl-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino-3-acetyl oxymethyl-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino-3-(2-FURARU carbonyl thiomethyl)-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino - 3-[(1, 2, 3-thiadiazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino - 3-[(1-methyl tetrazole-5-IRU) thiomethyl]-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino - 3-[(Z)-2-(1, 2, 3-thiadiazole-4-IRU) ethenyl]-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino - 3-[(5-methyl tetrazole-3-IRU) methyl]-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino - 3-[(Z)-2-(4-methyl thiazole-5-IRU) ethenyl]-3-cephem-4-carboxylic-acid trimethylsilyl, 7-amino - 3-[(1H- 1, 2, 3-triazole-5-IRU) thiomethyl thio]-3-cephem-4-carboxylic-acid trimethylsilyl etc. can be mentioned.

[0090] These compounds are 7-amino which can come to hand easily industrially. - After changing the 3rd place into a predetermined substituent by using a 3-acetyl oxymethyl-3-cephem-4-carboxylic acid as a start raw material, it can manufacture by esterifying a carboxyl group.

[0091] Moreover, as mentioned above, in order to obtain a peptide compound, it is suitable to use the amino acid compound derivative from which the carboxyl group was protected as an amine compound. Although it can use that there is no limit in any way if it is the compound from which it has an amino group and a carboxyl group in intramolecular, and the carboxyl group was protected by the protective group as an amino acid compound derivative from which this carboxyl group was protected, the compound from which the carboxyl group of available amino acid was generally easily protected as an industrial raw material as a reagent is used.

[0092] Here, the protective groups of a carboxyl group are the aralkyl radical of the carbon numbers 6-13, such as an alkyl group to the carbon numbers 1-4, such as a methyl group, an ethyl group, a propyl group, an isopropyl group, and t-butyl, benzyl, and a diphenyl methyl group, an amide group, N-methylamide radical, N-benzyl amide group, etc.

[0093] If the amino acid compound derivative from which the carboxyl group used suitably was protected is concretely illustrated in order to obtain a peptide compound alpha-amino butanoic acid, alpha-methyl alanine, an alanine, N-methyl alanine, The beta-alanine, gamma-amino butanoic acid, 5-

amino pentanoic acid, 6-amino hexanoic acid, 7-amino hexanoic acid, 8-amino octanoic acid, 11-amino undecanoic acid, 12-amino undecanoic acid, an arginine, an asparagine, an aspartic acid, beta-cyclohexyl alanine, a cyclohexyl glycine, S-acetamide cysteine, A S-tert-butyl cysteine, S-ethyl thiocysteine, a S-p-methoxybenzyl cysteine, S-trityl cysteine, a S-p-methylbenzyl homocysteine, A glutamine, an N-gamma-ethyl glutamine, a N-gamma-trityl glutamine, Glutamic acid, isoglutamine, a glycine, N-methyl glycine, a histidine, pi-benzyloxy methylhistidine, 1-methyl histidine, 3-methyl histidine, An isoleucine, a leucine, N-methyl leucine, a lysine, a N-epsilon-acetyl lysine, A N-epsilon-formyl leucine, a N-epsilon-benzyloxycarbonyl leucine, A methionine, a norleucine, a norvaline, an ornithine, 4-benzoyl FANIRU alanine, A FANIRU alanine, 4-chlorophenyl alanine, 4-fluoro phenylalanine, 4-benzyloxycarbonylamino phenylalanine, a gay phenylalanine, Phenylglycine, 4-hydroxy phenylglycine, a proline, a homoproline, 4-hydroxyproline, O-benzyl hydroxyproline, N-methyl glycine, Homoserine, O-benzyl homoserine, O-benzyl serine, a serine, - The compound which protected carboxyl groups, such as a tert-butyl serine, O-methyl serine, threonine, O-benzyl threonine, a tryptophan, a thyrosin, an O-tert-butyl thyrosin, O-benzyl thyrosin, and a valine, by said protective group can be mentioned.

[0094] Although there is not little what has asymmetrical carbon in the above-mentioned amino acid, in this invention, L bodies, D objects, and those mixture can be used that there is no limit in any way.

[0095] Although these compounds are usually available as a reagent and an industrial raw material When acquisition is difficult, after making the above-mentioned amino acid into acid chloride by a thionyl chloride etc., The alkyl alcoholic compound of the carbon numbers 1-4, such as a methanol, ethanol, propanol, isopropanol, and a tert-butanol, It can manufacture by making it react with the first class of the carbon numbers 1-10, such as an aralkyl alcoholic compound of the carbon numbers 7-13 of benzyl alcohol, diphenyl alcohol, etc., ammonia or monomethylamine, ethylamine, and benzylamine, or the second class amine.

[0096] Although especially a limit does not have the amount of the carboxylic-acid compound in the amide manufacture approach of this invention, and the amine compound used, since the reaction of the carboxyl group in the reaction (henceforth an amidation reaction) of this manufacture approach and the amino group is a stoichiometry reaction, In the reaction of the compounds which have each one radical at a time in intramolecular, respectively, it is usually desirable to use preferably 0.8-1.2 mols of amine compounds in 0.9-1.1 mols to one mol of carboxylic-acid compounds.

[0097] It is suitable to perform an amidation reaction in a solvent. The solvent which can be industrially used as a solvent at this time can use that there is no limit in any way. When these solvents are illustrated concretely, a water; tetrahydro furan, 1,4-dioxane, Ether, such as diethylether and tert-butyl methyl ether; Ethyl acetate, Nitril, such as ester; acetonitriles, such as propyl acetate and butyl acetate, and propionitrile; A methylene chloride, Halogenated aliphatic hydrocarbon, such as chloroform and a carbon tetrachloride; A methanol, Alcohols, such as ethanol, isopropanol, and a tert-butanol; An acetone, Carbonate [, such as ketones; dimethyl carbonate,], such as a methyl ethyl ketone and methyl isobutyl ketone; Benzene, Amides, such as halogenated-aromatics hydrocarbons; dimethylformamides [, such as an aromatic hydrocarbon; chlorobenzene,], such as toluene and a xylene, and dimethylacetamide; dimethyl sulfoxide etc. can be mentioned.

[0098] A tetrahydro furan since high condensation yield is especially expectable also in these solvents, Ether, such as 1,4-dioxane, diethylether, and tert-butyl methyl ether; Ethyl acetate, Nitril, such as ester; acetonitriles, such as propyl acetate and butyl acetate, and propionitrile; A methylene chloride, Halogenated aliphatic hydrocarbon, such as chloroform; A methanol, ethanol, Carbonate [, such as ketones; dimethyl carbonate,], such as alcohols; acetones, such as isopropanol and a tert-butanol, a methyl ethyl ketone, and methyl isobutyl ketone; aromatic hydrocarbon [, such as benzene toluene, and a xylene]; and water are adopted suitably. Even if it uses these solvents independently, and it mixes and uses it, they do not interfere at all.

[0099] the concentration in the solvent of the amide compound usually generated in order to cause trouble to stirring etc. especially as concentration of the carboxylic-acid compound in these solvents, and an amine compound if it is not economical and concentration is not much high, since the yield of the

amide compound per reaction will become small if concentration is not much low although not restricted -- 0.1 to 80 mass % -- what is necessary is just to choose so that it may become 1 - 60 mass % preferably

[0100] Next, the operating procedure of the amide manufacture approach of this invention etc. is explained.
[0101] As mentioned above, it sets to the amide manufacture approach of this invention. An amidation reaction Except using the water content quarternary ammonium salt of this invention as a condensing agent Although especially the operating procedure is not limited, it is [that what is necessary is just to carry out like the approach using the conventional condensing agent] suitable to mix and to make three kinds of reaction agents (namely, a condensing agent, a carboxylic-acid compound, and an amine compound) react from viewpoints, such as height of reaction yield and shortness of reaction time. In addition, each component does not necessarily need to exist in a form as it is in the system of reaction that what is necessary is to mix and just to make the three above-mentioned component react at this time. For example, it may neutralize and the carboxylic-acid compound and the amine compound may exist in the form of a salt.
[0102] In the above-mentioned approach, especially the mixed approach of the three above-mentioned kinds of reaction agents is not limited, but may add each component to coincidence at the system of reaction, may be mixed, and may add each reaction agent to the system of reaction one by one, and may be mixed. However, it is suitable to boil each reaction agent one by one into the reaction solvent beforehand maintained at predetermined temperature, and to add time amount as a dish, and to mix from the point of the height of operability and reaction yield. Although especially the addition sequence of each reaction agent is not restricted at this time, since a carboxylic-acid compound and an amine compound are considered that it is important to cause neutralization and to make a salt form in a solution, after adding a carboxylic-acid compound and an amine compound, it is usually common [this reaction] generally to add a condensing agent.
[0103] In order that neutralization may cut the addition sequence of a carboxylic-acid compound and an amine compound if both are mixed although the point is sufficient as whichever, generally heat of neutralization occurs. For this reason, since the inside of the system of reaction may be an elevated temperature, when a condensing agent is added immediately, a possibility that an amine compound and a condensing agent may react and yield may fall is immediately after addition of both compounds. For this reason, after addition of a condensing agent carries out addition mixing of a carboxylic-acid compound and the amine compound, it is desirable to lower beforehand the temperature of the solvent at the time of choosing at one's own discretion and supplying that the temperature of the system of reaction fell to predetermined temperature, or adding a carboxylic-acid compound and an amine compound enough.
[0104] Since the optimal temperature changes greatly with classes of the carboxylic-acid compound to be used and amine compound, the reaction temperature in an amidation reaction does not generally have ******, but if temperature is not much low, a reaction rate will become small, and when temperature is not much high, there is an inclination for the side reaction of an amine compound and a condensing agent reacting to occur. For this reason, especially as reaction temperature, it is suitable to adopt [-30-60-degree C] the temperature of the range of -20-50 degrees C.
[0105] Although what is necessary is just to determine suitably according to the class of the carboxylic-acid compound to be used and amine compound, if there are 0.1 - 8 hours of reaction time preferably as long as 1 to 6 hours, it is usually enough. Moreover, ordinary pressure, pressurization, or reduced pressure can carry out an amidation reaction.
[0106] Thus, as isolation of the obtained amide compound and the purification approach, the usual approach is used that there is no limit in any way. After reaction termination, when are illustrated concretely and water and an incompatible organic solvent are used as a reaction solvent, after aqueous acids, an alkaline water solution, and water wash reaction mixture, a solvent is distilled off and the approach of isolating and refining with recrystallization or a silica gel chromatography can be mentioned. Moreover, after reaction termination, when water and the dissolving organic solvent are used

as a reaction solvent, after exchanging for water and an incompatible organic solvent, it can isolate and refine by processing by the above-mentioned approach. Moreover, when water is used as a solvent, after adding water and an incompatible organic solvent and extracting an amide compound to an organic phase, it can isolate and refine by processing by the above-mentioned approach. Thus, an amide compound can be manufactured advantageously industrially.

[0107] (2) Explanation about the approach (henceforth the ester manufacture approach of this invention) of making a carboxylic-acid compound and an alcoholic compound reacting, and manufacturing an ester compound, using the water content quarternary ammonium salt of this invention as a condensing agent.

[0108] Although the ester manufacture approach of this invention can be performed like the approach of using the conventional condensing agent, except using the water content quarternary ammonium salt of this invention as a condensing agent, it is suitable for it to make the condensing agent which consists of water content quarternary ammonium salt of this invention, a carboxylic-acid compound, and an amine compound mix and react to the bottom of existence of the third class amine (henceforth an esterification reaction). By making the third class amine compound exist, it is possible to raise the reaction rate of esterification.

[0109] What is necessary is not to limit the class of water content quarternary ammonium salt used as a condensing agent in this invention, and especially its amount used, but just to determine them suitably according to the system of reaction at this time. Although each water content quarternary ammonium salt of this invention is usable to this manufacture approach, it is suitable 60 to quarternary-ammonium-salt 99 mass % which carried out the above-shown indication as what can expect condensation yield high [composition is easy especially, and] when it is moreover used as a condensing agent, and to use especially 65 to 97 mass % and 40 to water 1 mass %, and the thing that consists of 35 to 3 mass % especially. Moreover, since there is an inclination for a condensation reaction to finish incomplete generally if there is not much little amount of the condensing agent used, and to react with an alcoholic compound if there are not much many amounts, and for yield to fall about the amount used, it is suitable to carry out [from which 0.9-3 mols of quarternary ammonium salt become 0.95-2.5 mols especially to one mol of carboxylic-acid compounds] amount use.

[0110] Next, the carboxylic-acid compound used by this invention is explained.

[0111] Moreover, the aliphatic-carboxylic-acid compound same as a carboxylic-acid compound as the ability to use it by the amide manufacture approach of this invention, an aromatic-carboxylic-acid compound, the amino acid compound derivative from which the amino group was protected can be used. It is suitable to use the amino acid compound derivative by which the amino group was protected from a viewpoint that this reaction which advances under conditions mild also in these is very effective in esterification of a compound with a possibility that a decomposition reaction may advance with heat etc., and the same thing as what was illustrated by explanation of the amide manufacture approach of this invention as the example is mentioned.

[0112] Moreover, as an alcoholic compound used by the ester manufacture approach of this invention, the compound which has the hydroxyl group of the first class, the second class, and the third class can use it that there is no limit in any way. When the alcoholic compound which can be used suitably is illustrated concretely, a methanol, Ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, a 2-methyl-2-pentanol, A 3-methyl-3-pentanol, cyclo propanol, cyclopentanol, The fatty alcohol compound of the carbon numbers 1-10, such as a cyclohexanol and cyclo heptanol; A phenol, The aromatic alcohol compound of the carbon numbers 6-12, such as o-cresol, m-cresol, p-cresol, benzyl alcohol, 2-phenyl-1-ethanol, 1-phenyl-1-ethanol, and 3-phenyl-1-propanol, can be mentioned.

[0113] Also in these alcohol, the methanol with which especially an esterification reaction advances easily, ethanol, 1-propanol, 1-butanol, 1-pentanol, cyclo propanol, cyclopentanol, a cyclohexanol, cyclo heptanol, a phenol, p-cresol, benzyl alcohol, 2-phenyl-1-ethanol, and 3-phenyl-1-propanol are adopted suitably. Each of these alcoholic compounds is an industrial raw material or a compound available as a reagent.

[0114] Although especially the amount of the carboxylic-acid compound in the ester manufacture

approach of this invention and the alcoholic compound used is not limited, if it takes into consideration that the hydroxyl group of an alcoholic compound reacts in equivalent to the carboxyl group of a carboxylic-acid compound, and that the alcoholic compound itself serves as the function as a solvent, when using monohydric alcohol, if it usually uses the carboxyl group of a carboxylic-acid compound, and more than the equivalent, especially the upper limit will not be restricted. However, it is not much suitable to use an alcoholic compound to a carboxylic-acid compound, so that the yield of the ester compound per batch decreases, and the concentration of the carboxylic-acid compound in an alcoholic compound may become more than 0.1 mass % since it is not economical if there is much amount of the alcoholic compound used.

[0115] Said the third class amine compound used if needed by the ester manufacture approach of this invention can be used that there is no limit in any way, if it is the compound which has the amino group of the third class. When the third class amine compound which can be used suitably is illustrated concretely, 4-methyl morpholine, 4-ethyl morpholine, N-methyl pyrrolidine, N-ethyl pyrrolidine, N-methyl piperidine, N-ethyl piperidine, N-methyl indoline, N-methyl iso indoline, triethylamine, tributylamine,

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